

Charles M. Lizza  
William C. Baton  
SAUL EWING LLP  
One Riverfront Plaza, Suite 1520  
Newark, NJ 07102-5426  
(973) 286-6700  
clizza@saul.com

OF COUNSEL:

Raymond N. Nimrod  
Matthew A. Traupman  
Catherine T. Mattes  
QUINN EMANUEL URQUHART & SULLIVAN, LLP  
51 Madison Avenue  
New York, NY 10010

*Attorneys for Plaintiffs*  
*Mitsubishi Tanabe Pharma Corp.,*  
*Janssen Pharmaceuticals, Inc. Janssen Pharmaceutica NV,*  
*Janssen Research and Development, LLC,*  
*and Cilag GmbH International*

**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

MITSUBISHI TANABE PHARMA  
CORPORATION, JANSSEN  
PHARMACEUTICALS, INC., JANSSEN  
PHARMACEUTICA NV, JANSSEN  
RESEARCH AND DEVELOPMENT, LLC, and  
CILAG GMBH INTERNATIONAL,

Plaintiffs,

v.

AUROBINDO PHARMA USA, INC., INVAGEN  
PHARMACEUTICALS, INC., MACLEODS  
PHARMACEUTICALS, LTD., and MACLEODS  
PHARMA USA, INC.,

Defendants.

Civil Action No. \_\_\_\_\_

**COMPLAINT FOR PATENT  
INFRINGEMENT**

(Filed Electronically)

Plaintiffs Mitsubishi Tanabe Pharma Corp. (“MTPC”), Janssen Pharmaceuticals, Inc. (“JPI”), Janssen Pharmaceutica NV (“JNV”), Janssen Research and Development, LLC (“JRD”), and Cilag GmbH International (“Cilag”) (collectively, “Plaintiffs”), by their attorneys, for their complaint against Aurobindo Pharma USA, Inc. (“Aurobindo”), InvaGen Pharmaceuticals, Inc. (“InvaGen”), Macleods Pharmaceuticals, Ltd. (“Macleods India”), and Macleods Pharma USA, Inc. (“Macleods USA”) (collectively, “Defendants”) allege as follows:

### **NATURE OF THE ACTION**

1. This is a civil action for infringement of United States Patent Nos. 7,943,582 (the “582 patent”) and 8,513,202 (the “202 patent”) (collectively, the “Patents-in-suit”) under the patent laws of the United States, 35 U.S.C. §100, *et seq.* This action arises from Aurobindo’s filing of Abbreviated New Drug Application (“ANDA”) No. 210386 (“the Aurobindo ANDA”) with the United States Food and Drug Administration (“FDA”) seeking approval to commercially market generic versions of JPI’s 100 mg and 300 mg INVOKANA® drug product (“the Aurobindo ANDA Product”), InvaGen’s filing of ANDA No. 210350 (“the InvaGen ANDA”) with the FDA seeking approval to commercially market generic versions of JPI’s 50 mg/500 mg; 50 mg/1 g; 150 mg/500 mg; and 150 mg/1 g INVOKAMET® drug product (“the InvaGen ANDA Product”), and Macleods India’s filing of ANDA No. 210380 (“the Macleods ANDA”) with the FDA seeking approval to commercially market generic versions of JPI’s 50 mg/500 mg; 50 mg/1 g; 150 mg/500 mg; and 150 mg/1 g INVOKAMET® drug product (“the Macleods ANDA Product”) prior to the expiration of the Patents-in-suit.

## THE PARTIES

2. MTPC is a corporation organized and existing under the laws of Japan, having an office and place of business at 3-2-10, Dosho-machi, Chuo-ku, Osaka 541-8505, Japan.

3. JPI is a corporation organized and existing under the laws of the State of Pennsylvania, having its principal place of business at 1125 Trenton-Harbourton Road, Titusville, New Jersey 08560.

4. JNV is a corporation organized and existing under the laws of Belgium, having its principal place of business at Turnhoutseweg, 30, 2340 Beerse, Belgium.

5. JRD is a corporation organized and existing under the laws of the State of New Jersey, having its principal place of business at 920 Route 202, Raritan, New Jersey 08869.

6. Cilag is a company organized and existing under the laws of Switzerland, having its principal place of business at Gubelstrasse 34, 6300, Zug, Switzerland.

7. On information and belief, defendant Aurobindo is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 6 Wheeling Road, Dayton, New Jersey 08810.

8. On information and belief, defendant InvaGen is a corporation organized and existing under the laws of the State of New York, having its principal place of business at 7 Oser Avenue, Hauppauge, NY 11788.

9. On information and belief, defendant Macleods India is a corporation organized and existing under the laws of India, having its principal place of business at Atlanta Arcade, Marol Church Road, Andheri (East), Mumbai, 40059, India.

10. On information and belief, defendant Macleods USA is a corporation organized under the laws of the State of Delaware, having its principal place of business at 666 Plainsboro Road, Building 200, Suite 230, Plainsboro, New Jersey 08536.

### **THE PATENTS-IN-SUIT**

11. On May 17, 2011, the United States Patent and Trademark Office (“USPTO”) duly and lawfully issued the ’582 patent, entitled “Crystalline form of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate” to MTPC as assignee of inventors Sumihiro Nomura and Eiji Kawanishi. A copy of the ’582 patent is attached as Exhibit A.

12. JPI, JRD, and Cilag are exclusive licensees of the ’582 patent.

13. JNV is an exclusive sublicensee of the ’582 patent.

14. On August 20, 2013, the USPTO duly and lawfully issued the ’202 patent, entitled “Crystalline form of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate” to MTPC as assignee of inventors Sumihiro Nomura and Eiji Kawanishi. A copy of the ’202 patent is attached as Exhibit B.

15. JPI, JRD, and Cilag are exclusive licensees of the ’202 patent.

16. JNV is an exclusive sublicensee of the ’202 patent.

### **THE INVOKANA® AND INVOKAMET® DRUG PRODUCTS**

17. JPI holds approved New Drug Application (“NDA”) No. 204042 for canagliflozin tablets, which are prescribed and sold under the trademark INVOKANA®. INVOKANA® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

18. JPI holds approved NDA No. 204353 for canagliflozin and metformin hydrochloride tablets, which are prescribed and sold under the trademark INVOKAMET®. INVOKAMET® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients who are already being treated with both canagliflozin and metformin.

19. The claims of the Patents-in-suit cover, *inter alia*, certain polymorphic forms of canagliflozin.

20. Pursuant to 21 U.S.C. § 355(b)(1), and attendant FDA regulations, the '582 and '202 patents are listed in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to both INVOKANA® and INVOKAMET®.

### **SUBJECT MATTER JURISDICTION**

21. This action arises under the patent laws of the United States, 35 U.S.C. §§ 100, *et seq.*, and this Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

### **PERSONAL JURISDICTION AND VENUE OVER AUROBINDO**

22. This Court has personal jurisdiction over Aurobindo because, *inter alia*, Aurobindo has committed an act of patent infringement under 35 U.S.C. § 271(e)(2) and intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will lead to foreseeable harm and injury to Plaintiffs in New Jersey. For example, on information and belief, following approval of the Aurobindo ANDA, Aurobindo will make, use, import, sell, and/or offer for sale the Aurobindo ANDA Product in the United States, including in New Jersey, prior to the expiration of the Patents-in-suit.

23. This Court also has personal jurisdiction over Aurobindo because, *inter alia*, this action arises from actions of Aurobindo directed toward New Jersey. For example, Aurobindo's counsel sent a letter dated May 24, 2017 to JPI, a corporation with its principal place of business in this Judicial District stating that Aurobindo had submitted ANDA No. 210386 seeking approval to commercially manufacture, use, import, offer for sale, and sell the Aurobindo ANDA Product prior to the expiration of the Patents-in-suit. If Aurobindo succeeds in obtaining FDA approval, it would sell its Aurobindo ANDA Product in New Jersey and other states, causing injury to Plaintiffs in New Jersey.

24. The Court also has personal jurisdiction over Aurobindo because Aurobindo has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, Aurobindo regularly and continuously transacts business within New Jersey, including by maintaining its principal place of business in New Jersey and by selling pharmaceutical products in New Jersey. On information and belief, Aurobindo derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey.

25. On information and belief, Aurobindo has continuously placed its products into the stream of commerce for distribution and consumption in the State of New Jersey and throughout the United States, and thus has engaged in the regular conduct of business within this Judicial District.

26. On information and belief, Aurobindo derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

27. On information and belief, Aurobindo has previously invoked, stipulated and/or consented to personal jurisdiction in this Judicial District in numerous prior patent cases.

28. Aurobindo has previously been sued in this Judicial District and has availed itself of New Jersey courts through the assertion of counterclaims in suits brought in New Jersey, including *Shionogi & Co., Ltd., et al. v. Aurobindo Pharma Ltd., et al.*, Civil Action No. 15-0319 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims); *Takeda Pharmaceutical Company Ltd., et al. v. Aurobindo Pharma Ltd., et al.*, Civil Action No. 15-7635 (D.N.J) (not contesting personal jurisdiction or venue and asserting counterclaims); and *Astrazeneca Pharmaceuticals LP et al. v. Aurobindo Pharma Limited, Inc. et al.*, Civil Action No. 07-6020 (D.N.J.) (admitting to personal jurisdiction and venue and asserting counterclaims).

29. Venue is proper for Aurobindo under 28 U.S.C. § 1400(b) because Aurobindo has a regular and established place of business in New Jersey, and has or will commit acts of infringement in New Jersey, as set forth in paragraphs 22-23.

#### **PERSONAL JURISDICTION AND VENUE OVER INVAGEN**

30. This Court has personal jurisdiction over InvaGen because, *inter alia*, InvaGen has committed an act of patent infringement under 35 U.S.C. § 271(e)(2) and intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will lead to foreseeable harm and injury to Plaintiffs in New Jersey. For example, on information and belief, following approval of the InvaGen ANDA, InvaGen will make, use, import, sell, and/or offer for sale the InvaGen ANDA Product in the United States, including in New Jersey, prior to the expiration of the Patents-in-suit.

31. This Court also has personal jurisdiction over InvaGen because, *inter alia*, this action arises from actions of InvaGen directed toward New Jersey. For example, InvaGen's counsel sent a letter dated May 23, 2017 to JPI, a corporation with its principal place of business

in this Judicial District stating that InvaGen had submitted ANDA No. 210350 seeking approval to commercially manufacture, use, import, offer for sale, and sell the InvaGen ANDA Product prior to the expiration of the Patents-in-suit. If InvaGen succeeds in obtaining FDA approval, it would sell its InvaGen ANDA Product in New Jersey and other states, causing injury to Plaintiffs in New Jersey.

32. The Court also has personal jurisdiction over InvaGen because InvaGen has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, InvaGen regularly and continuously transacts business within New Jersey, including by selling pharmaceutical products in New Jersey. On information and belief, InvaGen derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey.

33. On information and belief, InvaGen has continuously placed its products into the stream of commerce for distribution and consumption in the State of New Jersey and throughout the United States, and thus has engaged in the regular conduct of business within this Judicial District.

34. On information and belief, InvaGen derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

35. On information and belief, InvaGen has previously invoked, stipulated and/or consented to personal jurisdiction in this Judicial District in numerous prior patent cases.

36. InvaGen has previously been sued in this Judicial District and has availed itself of New Jersey courts through the assertion of counterclaims in suits brought in New Jersey,

including *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. HEC Pharm Group, et al.*, Civil Action No. 15-5982 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims); *Shire Development LLC, et al. v. InvaGen Pharmaceuticals, Inc.*, Civil Action No. 15-367 (D.N.J.) (consenting to transfer to this Judicial District and asserting counterclaims); and *Roxane Labs., Inc. v. Chamber Pharmaceuticals, Inc., et al.*, Civil Action No. 14-4042 (D.N.J.) (arguing for transfer to this Judicial District, admitting to being subject to personal jurisdiction for the action, admitting to proper venue, and asserting counterclaims).

37. InvaGen has previously submitted to the jurisdiction of this Court and has availed itself of the legal protections of the State of New Jersey, having previously transferred a case into this Judicial District by stating that “personal jurisdiction exists in New Jersey over . . . InvaGen” and “[t]he place where InvaGen’s research, development, and manufacturing and sales decisions occurred is InvaGen’s headquarters in Hauppauge, NY, less than 60 miles from the federal court in Newark, NJ.” *Roxane Laboratories, Inc. v. Camber Pharmaceuticals, Inc. & InvaGen Pharmaceuticals, Inc.*, Civil Action No. 14-4042 (D.N.J. Apr. 4, 2014) (D.I. 28 at 18); *see also Roxane Laboratories, Inc. v. Camber Pharmaceuticals, Inc. & InvaGen Pharmaceuticals, Inc.*, Civil Action No. 14-0232 (S.D. Ohio Apr. 4, 2014) (D.I. 28 at 18).

38. Venue is also proper in this Court for InvaGen because InvaGen has consented to venue for purposes of this action only.

#### **PERSONAL JURISDICTION AND VENUE OVER MACLEODS INDIA AND MACLEODS USA**

39. On information and belief, Macleods India operates as a single, integrated generic pharmaceutical manufacturer. For example, on Macleods India’s website, Macleods USA is described as “the U.S. division of Macleods Pharmaceuticals, LTD, a developer and

manufacturer of Generic Active Pharmaceutical Ingredients (API) and Finished Dosage Forms.” [Macleods US, www.macleodspharma.com/UnitedStates.asp](http://www.macleodspharma.com/UnitedStates.asp) (last visited July 3, 2017).

40. This Court has personal jurisdiction over Macleods India because, *inter alia*, Macleods India has committed an act of patent infringement under 35 U.S.C. § 271(e)(2) and intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will lead to foreseeable harm and injury to Plaintiffs in New Jersey. For example, on information and belief, following approval of the Macleods ANDA, Macleods India will make, use, import, sell, and/or offer for sale the Macleods ANDA Product in the United States, including in New Jersey, prior to the expiration of the Patents-in-suit.

41. This Court also has personal jurisdiction over Macleods India because, *inter alia*, this action arises from actions of Macleods India directed toward New Jersey. For example, Macleods’s counsel sent a letter dated May 23, 2017 to JPI, a corporation with its principal place of business in this Judicial District stating that Macleods had submitted ANDA No. 210380 seeking approval to commercially manufacture, use, import, offer for sale, and sell the Macleods ANDA Product prior to the expiration of the Patents-in-suit. If Macleods succeeds in obtaining FDA approval, it would sell its Macleods ANDA Product in New Jersey and other states, causing injury to Plaintiffs in New Jersey.

42. This Court also has personal jurisdiction over Macleods India because Macleods India has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, Macleods India regularly and continuously transacts business within New Jersey, including by selling pharmaceutical products in New Jersey. On information and belief, Macleods India derives substantial revenue from the sale of those products in New Jersey and

has availed itself of the privilege of conducting business within New Jersey. For example, Macleods India's website states that "Macleods has received FDA approval on 9 [ANDAs] and has another 60 filed and awaiting approval." Macleods US, <http://www.macleodspharma.com/UnitedStates.asp> (last visited July 3, 2017).

43. On information and belief, Macleods India has continuously placed its products into the stream of commerce for distribution and consumption in the State of New Jersey, and throughout the United States, and thus has engaged in the regular conduct of business within this Judicial District.

44. On information and belief, Macleods India derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

45. On information and belief, Macleods India has previously invoked, stipulated, and/or consented to personal jurisdiction in this Judicial District in numerous prior patent cases.

46. Macleods India has previously been sued in this Judicial District and has availed itself of New Jersey courts through the assertion of counterclaims in suits brought in New Jersey, including *AstraZeneca AB, et al. v. Macleods Pharmaceuticals Ltd., et al.*, Civil Action No. 16-1682 (D.N.J.) (consenting to personal jurisdiction and venue for the purposes of the action and asserting counterclaims); and *Otsuka Pharmaceutical Co., Ltd. v. Macleods Pharmaceuticals Ltd., et al.*, Civil Action No. 15-5109 (D.N.J.) (consenting to personal jurisdiction and venue for the purposes of the action and asserting counterclaims).

47. On information and belief, Macleods USA is a wholly owned subsidiary of Macleods India and is controlled and dominated by Macleods India. Macleods US,

<http://www.macleodspharma.com/UnitedStates.asp> (last visited July 3, 2017) (“Macleods Pharma USA is the U.S. division of Macleods Pharmaceuticals, LTD.”). On information and belief, Macleods India is a “truly . . . global pharmaceutical company.” Macleods, <http://www.macleodspharma.com/default.asp> (last visited July 3, 2017). On information and belief, Macleods Pharmaceuticals is “a vertically integrated global pharmaceutical company” with “more than 10,000 professionally qualified employees across the globe.” *Id.*

48. On information and belief, Macleods USA, Inc. is in the business, *inter alia*, of developing, manufacturing, and obtaining regulatory approval of generic copies of branded pharmaceutical products for distribution and sale throughout the United States, including within this Judicial District. Macleods US, [www.macleodspharma.com/UnitedStates.asp](http://www.macleodspharma.com/UnitedStates.asp) (last visited July 3, 2017) (“Macleods Pharma USA is the U.S. division of Macleods Pharmaceuticals, LTD, a developer and manufacturer of Generic Active Pharmaceutical Ingredients (API) and Finished Dosage Forms.”). On information and belief, Macleods USA markets, distributes, sells, and/or offers for sale generic drugs throughout the United States and in New Jersey at the direction of, under the control of, and for the direct benefit of Macleods India. On information and belief, Macleods USA “is based in Plainsboro, NJ.” *Id.* This Court has jurisdiction over Macleods India because, on information and belief, Macleods India is the parent corporation of Macleods USA.

49. In the alternative, this Court has jurisdiction over Macleods India because the requirements of Federal Rule of Civil Procedure 4(k)(2)(A) are met as (a) Plaintiffs’ claims arise under federal law; (b) Macleods India is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Macleods India has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting an ANDA to the

FDA and/or manufacturing and/or selling pharmaceutical products distributed throughout the United States, such that this Court's exercise of jurisdiction over Macleods India satisfies due process.

50.     Venue is proper for Macleods India under 28 U.S.C. §§ 1391 and/or 1400(b), including because, *inter alia*, Macleods India is subject to personal jurisdiction in this Judicial District, as set forth above, has committed an act of infringement and will commit further acts of infringement in this Judicial District, as set forth in paragraphs 40-41 above, continuously transacts business in this Judicial District, as set forth in paragraph 42 above, and has a continuous and permanent presence in this Judicial District through its subsidiary, Macleods USA.

51.     This Court has personal jurisdiction over Macleods USA because, *inter alia*, Macleods USA intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will lead to foreseeable harm and injury to Plaintiffs in New Jersey. For example, on information and belief, following approval of the Macleods ANDA, Macleods USA will work in concert with Macleods India to make, use, import, sell, and/or offer for sale the Macleods ANDA Product in the United States, including in New Jersey, prior to the expiration of the Patent-in-suits. On information and belief, Macleods USA is registered as a wholesaler in the State of New Jersey (No. 5004370). *See* New Jersey Registration and Verification, <http://web.doh.state.nj.us/apps2/FoodDrugLicense/fdList.aspx> (last visited July 1, 2017).

52.     This Court also has personal jurisdiction over Macleods USA because, *inter alia*, this action arises from actions of Macleods USA directed toward New Jersey, and because Macleods USA has purposefully availed itself of the rights and benefits of New Jersey

law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, Macleods USA maintains its principal place of business in New Jersey and regularly and continuously transacts business within New Jersey, including by selling pharmaceutical products in New Jersey. On information and belief, Macleods USA derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey. On information and belief, Macleods USA is registered as a wholesaler in the State of New Jersey (No. 5004370). *See New Jersey Registration and Verification*, <http://web.doh.state.nj.us/apps2/FoodDrugLicense/fdList.aspx> (last visited July 3, 2017).

53. On information and belief, Macleods USA has continuously placed its products into the stream of commerce for distribution and consumption in the State of New Jersey, and throughout the United States, and thus has engaged in the regular conduct of business within this Judicial District.

54. On information and belief, Macleods USA derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

55. On information and belief, Macleods USA has previously invoked, stipulated, and/or consented to personal jurisdiction in this Judicial District in numerous prior patent cases.

56. Macleods USA has previously been sued in this Judicial District and has availed itself of New Jersey courts through the assertion of counterclaims in suits brought in New Jersey, including *AstraZeneca AB, et al. v. Macleods Pharmaceuticals Ltd., et al.*, Civil Action No. 16-1682 (D.N.J) (consenting to personal jurisdiction and venue for the purposes of

the action and asserting counterclaims); and *Otsuka Pharmaceutical Co., Ltd. v. Macleods Pharmaceuticals Ltd., et al.*, Civil Action No. 15-5109 (D.N.J.) (consenting to personal jurisdiction and venue for the purposes of the action and asserting counterclaims).

57. Venue is proper for Macleods USA under 28 U.S.C. § 1400(b) because, *inter alia*, Macleods USA has a regular and established place of business in New Jersey and will commit further acts of infringement in this Judicial District, as set forth in paragraphs 51-52 above.

#### **AUROBINDO'S INFRINGING ANDA SUBMISSION**

58. On or about May 25, 2017, JPI received from Aurobindo's counsel a letter, dated May 24, 2017 ("Aurobindo May 24 Letter"), stating that Aurobindo had submitted the Aurobindo ANDA to the FDA seeking approval to market the Aurobindo ANDA Product before the expiration of the Patents-in-suit. MTPC received the Aurobindo May 24 Letter on or about May 30, 2017.

59. Aurobindo specifically directed the Aurobindo May 24 Letter to JPI's headquarters in Raritan, New Jersey, within this Judicial District.

60. The Aurobindo ANDA Product is intended to be a generic version of INVOKANA®.

61. The Aurobindo May 24 Letter alleges that the Aurobindo ANDA Product does not infringe the '582 patent or the '202 patent. Notwithstanding these allegations, on information and belief, discovery/testing will show that the Aurobindo ANDA Product infringes the Patents-in-suit.

62. This action is being commenced before the expiration of 45 day from the date MTPC and JPI received the Aurobindo May 24 Letter.

### **INVAGEN'S INFRINGING ANDA SUBMISSION**

63. On or about May 24, 2017, JPI received from InvaGen's counsel a letter, dated May 23, 2017 ("InvaGen May 23 Letter"), stating that InvaGen had submitted the InvaGen ANDA to the FDA seeking approval to market the InvaGen ANDA Product before the expiration of the Patents-in-suit. MTPC received the InvaGen May 23 Letter on or about May 26, 2017.

64. InvaGen specifically directed the InvaGen May 23 Letter to JPI's headquarters in Raritan, New Jersey, within this Judicial District.

65. The InvaGen ANDA Product is intended to be a generic version of INVOKAMET®.

66. The InvaGen May 23 Letter alleges that the InvaGen ANDA Product does not infringe the '582 patent or the '202 patent. Notwithstanding these allegations, on information and belief, discovery/testing will show that the InvaGen ANDA Product infringes the Patents-in-suit.

67. The InvaGen May 23 Letter alleges that the '582 patent is invalid.

68. This action is being commenced before the expiration of 45 days from the date MTPC and JPI received the InvaGen May 23 Letter.

### **MACLEODS INDIA'S INFRINGING ANDA SUBMISSION**

69. On or about May 24, 2017, JPI received from Macleods India's counsel a letter, dated May 23, 2017 ("Macleods May 23 Letter"), stating that Macleods India had submitted the Macleods ANDA to the FDA seeking approval to market the Macleods ANDA Product before the expiration of the Patents-in-suit. MTPC received the Macleods May 23 Letter on or about May 26, 2017.

70. Macleods India specifically directed the Macleods May 23 Letter to JPI's headquarters in Raritan, New Jersey, within this Judicial District.

71. The Macleods ANDA Product is intended to be a generic version of INVOKAMET®.

72. On information and belief, following FDA approval of Macleod's ANDA, Macleods India and Macleods USA will work in concert with one another to make, use, sell, or offer to sell the Macleods ANDA Product throughout the United States, or import such generic products into the United States.

73. The Macleods May 23 Letter alleges that the Macleods ANDA Product does not infringe the '582 patent or the '202 patent. Notwithstanding these allegations, on information and belief, discovery/testing will show that the Macleods ANDA Product infringes the Patents-in-suit.

74. This action is being commenced before the expiration of 45 days from the date MTPC and JPI received the Macleods May 23 Letter.

**COUNT I**  
**Infringement of U.S. Patent No. 7,943,582 by Eurobindo**

75. Plaintiffs repeat and reallege paragraphs 1-74 above as if fully set forth herein.

76. By filing its ANDA No. 210386 for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of the Eurobindo ANDA Product before the expiration of the '582 patent, Eurobindo committed an act of infringement under 35 U.S.C. § 271(e)(2).

77. On information and belief, discovery/testing will show that if Eurobindo commercially makes, uses, offers to sell, or sells the Eurobindo ANDA Product within the United States, or imports the Eurobindo ANDA Product into the United States, or induces or

contributes to any such conduct during the term of the '582 patent, it would further infringe at least claims 1, 6, and 7 of the '582 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

78. Aurobindo has had knowledge of the '582 patent since at least the date it submitted the Aurobindo ANDA.

79. Plaintiffs will be irreparably harmed if Aurobindo is not enjoined from infringing the '582 patent. Plaintiffs do not have an adequate remedy at law.

**COUNT II**  
**Infringement of U.S. Patent No. 8,513,202 by Aurobindo**

80. Plaintiffs repeat and reallege paragraphs 1-79 above as if fully set forth herein.

81. By filing its ANDA No. 210386 for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of the Aurobindo ANDA Product before the expiration of the '202 patent, Aurobindo committed an act of infringement under 35 U.S.C. § 271(e)(2).

82. On information and belief, discovery/testing will show that if Aurobindo commercially makes, uses, offers to sell, or sells the Aurobindo ANDA Product within the United States, or imports the Aurobindo ANDA Product into the United States, or induces or contributes to any such conduct during the term of the '202 patent, it would further infringe at least claims 1 and 3-5 of the '202 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

83. Aurobindo has had knowledge of the '202 patent since at least the date it submitted the Aurobindo ANDA.

84. Plaintiffs will be irreparably harmed if Aurobindo is not enjoined from infringing the '202 patent. Plaintiffs do not have an adequate remedy at law.

**COUNT III**  
**Infringement of U.S. Patent No. 7,943,582 by InvaGen**

85. Plaintiffs repeat and reallege paragraphs 1-84 above as if fully set forth herein.

86. By filing its ANDA No. 210350 for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of the InvaGen ANDA Product before the expiration of the '582 patent, InvaGen committed an act of infringement under 35 U.S.C. § 271(e)(2).

87. On information and belief, discovery/testing will show that if InvaGen commercially makes, uses, offers to sell, or sells the InvaGen ANDA Product within the United States, or imports the InvaGen ANDA Product into the United States, or induces or contributes to any such conduct during the term of the '582 patent, it would further infringe at least claims 1, 6, and 7 of the '582 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

88. InvaGen has had knowledge of the '582 patent since at least the date it submitted the InvaGen ANDA.

89. Plaintiffs will be irreparably harmed if InvaGen is not enjoined from infringing the '582 patent. Plaintiffs do not have an adequate remedy at law.

**COUNT IV**  
**Infringement of U.S. Patent No. 8,513,202 by InvaGen**

90. Plaintiffs repeat and reallege paragraphs 1-89 above as if fully set forth herein.

91. By filing its ANDA No. 210350 for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United

States of the InvaGen ANDA Product before the expiration of the '202 patent, InvaGen committed an act of infringement under 35 U.S.C. § 271(e)(2).

92. On information and belief, discovery/testing will show that if InvaGen commercially makes, uses, offers to sell, or sells the InvaGen ANDA Product within the United States, or imports the InvaGen ANDA Product into the United States, or induces or contributes to any such conduct during the term of the '202 patent, it would further infringe at least claims 1 and 3-5 of the '202 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

93. InvaGen has had knowledge of the '202 patent since at least the date it submitted the InvaGen ANDA.

94. Plaintiffs will be irreparably harmed if InvaGen is not enjoined from infringing the '202 patent. Plaintiffs do not have an adequate remedy at law.

**COUNT V**  
**Infringement of U.S. Patent No. 7,943,582 by Macleods India and Macleods USA**

95. Plaintiffs repeat and reallege paragraphs 1-94 above as if fully set forth herein.

96. By filing its ANDA No. 210380 for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of the Macleods ANDA Product before the expiration of the '582 patent, Macleods India committed an act of infringement under 35 U.S.C. § 271(e)(2).

97. On information and belief, discovery/testing will show that if Macleods India and/or Macleods USA commercially makes, uses, offers to sell, or sells the Macleods ANDA Product within the United States, or imports the Macleods ANDA Product into the United States, or induces or contributes to any such conduct during the term of the '582 patent, it

would further infringe at least claims 1, 6, and 7 of the '582 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

98. Macleods India has had knowledge of the '582 patent since at least the date Macleods India submitted the Macleods ANDA. Macleods USA will have knowledge of the '582 patent no later than the date it is served with this complaint.

99. Plaintiffs will be irreparably harmed if Macleods India and Macleods USA are not enjoined from infringing the '582 patent. Plaintiffs do not have an adequate remedy at law.

**COUNT VI**  
**Infringement of U.S. Patent No. 8,513,202 by Macleods India and Macleods USA**

100. Plaintiffs repeat and reallege paragraphs 1-99 above as if fully set forth herein.

101. By filing its ANDA No. 210380 for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of the Macleods ANDA Product before the expiration of the '202 patent, Macleods India committed an act of infringement under 35 U.S.C. § 271(e)(2).

102. On information and belief, discovery/testing will show that if Macleods India and/or Macleods USA commercially makes, uses, offers to sell, or sells the Macleods ANDA Product within the United States, or imports the Macleods ANDA Product into the United States, or induces or contributes to any such conduct during the term of the '202 patent, it would further infringe at least claims 1 and 3-5 of the '202 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

103. Macleods India has had knowledge of the '202 patent since at least the date Macleods India submitted the Macleods ANDA. Macleods USA will have knowledge of the '582 patent no later than the date it is served with this complaint.

104. Plaintiffs will be irreparably harmed if Macleods India and Macleods USA are not enjoined from infringing the '202 patent. Plaintiffs do not have an adequate remedy at law.

#### **PRAYER FOR RELIEF**

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A Judgment that Aurobindo has infringed one or more claims of the '582 patent by filing ANDA No. 210386;

B. A Judgment that Aurobindo has infringed, and that Aurobindo's making, using, selling, offering to sell, or importing the Aurobindo ANDA Product would constitute infringement of one or more claims of the '582 patent, and/or induce or contribute to the infringement of one or more claims of the '582 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

C. A permanent injunction restraining and enjoining Aurobindo, and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the Aurobindo ANDA Product until after the expiration of the '582 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

D. An Order that the effective date of any approval of ANDA No. 210386 relating to the Aurobindo ANDA Product be a date that is not earlier than the expiration date of

the '582 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

E. A Judgment that Aurobindo has infringed one or more claims of the '202 patent by filing ANDA No. 210386;

F. A Judgment that Aurobindo has infringed, and that Aurobindo's making, using, selling, offering to sell, or importing the Aurobindo ANDA Product would constitute infringement of one or more claims of the '202 patent, and/or induce or contribute to the infringement of one or more claims of the '202 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

G. A permanent injunction restraining and enjoining Aurobindo, and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the Aurobindo ANDA Product until after the expiration of the '202 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

H. An Order that the effective date of any approval of ANDA No. 210386 relating to the Aurobindo ANDA Product be a date that is not earlier than the expiration date of the '202 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

I. A Judgment that InvaGen has infringed one or more claims of the '582 patent by filing ANDA No. 210350;

J. A Judgment that InvaGen has infringed, and that InvaGen's making, using, selling, offering to sell, or importing the InvaGen ANDA Product would constitute infringement of one or more claims of the '582 patent, and/or induce or contribute to

infringement of one or more claims of the '582 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

K. A permanent injunction restraining and enjoining InvaGen, and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the InvaGen ANDA Product until after the expiration of the '582 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

L. An Order that the effective date of any approval of NDA No. 210350 relating to the InvaGen ANDA Product be a date that is not earlier than the expiration date of the '582 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

M. A Judgment that InvaGen has infringed one or more claims of the '202 patent by filing ANDA No. 210350;

N. A Judgment that InvaGen has infringed, and that InvaGen's making, using, selling, offering to sell, or importing the InvaGen ANDA Product would constitute infringement of one or more claims of the '202 patent, and/or induce or contribute to infringement of one or more claims of the '202 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

O. A permanent injunction restraining and enjoining InvaGen Pharmaceuticals, Inc., and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the InvaGen ANDA

Product until after the expiration of the '202 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

P. An Order that the effective date of any approval of ANDA No. 210350 relating to the InvaGen ANDA Product be a date that is not earlier than the expiration date of the '202 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

Q. A Judgment that Macleods India has infringed one or more claims of the '582 patent by filing ANDA No. 210380;

R. Judgment that Macleods India and Macleods USA have infringed, and that Macleods India's and/or Macleods USA's making, using, selling, offering to sell, or importing the Macleods ANDA Product would constitute infringement of one or more claims of the '582 patent, and/or induce or contribute to the infringement of one or more claims of the '582 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

S. A permanent injunction restraining and enjoining Macleods India and Macleods USA, and their officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the Macleods ANDA Product until after the expiration of the '582 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

T. An Order that the effective date of any approval of ANDA No. 210380 relating to the Macleods ANDA Product be a date that is not earlier than the expiration date of the '582 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

U. A Judgment that Macleods India has infringed one or more claims of the '202 patent by filing ANDA No. 210380;

V. A Judgment that Macleods India and Macleods USA have infringed, and that Macleods India's and/or Macleods USA's making, using, selling, offering to sell, or importing the Macleods ANDA Product would constitute infringement of one or more claims of the '202 patent, and/or induce or contribute to the infringement of one or more claims of the '202 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

W. A permanent injunction restraining and enjoining Macleods India and Macleods USA, and their officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the Macleods ANDA Product until after the expiration of the '202 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

X. An Order that the effective date of any approval of ANDA No. 210380 relating to the Macleods ANDA Product be a date that is not earlier than the expiration date of the '202 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled; and

Y. Such other and further relief as the Court may deem just and proper.

Dated: July 7, 2017

OF COUNSEL:

Raymond N. Nimrod  
Matthew A. Traupman  
Catherine T. Mattes  
QUINN EMANUEL  
URQUHART & SULLIVAN, LLP  
51 Madison Avenue  
New York, NY 10010

By: s/ Charles M. Lizza

Charles M. Lizza  
William C. Baton  
SAUL EWING LLP  
One Riverfront Plaza, Suite 1520  
Newark, NJ 07102-5426  
(973) 286-6700  
clizza@saul.com

*Attorneys for Plaintiffs*  
*Mitsubishi Tanabe Pharma Corp.,*  
*Janssen Pharmaceuticals, Inc. Janssen*  
*Pharmaceutica NV, Janssen Research*  
*and Development, LLC, and Cilag*  
*GmbH International*

**CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1**

I hereby certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: July 7, 2017

By: s/ Charles M. Lizza

Charles M. Lizza  
William C. Baton  
SAUL EWING LLP  
One Riverfront Plaza, Suite 1520  
Newark, NJ 07102-5426  
(973) 286-6700  
clizza@saul.com

OF COUNSEL:

Raymond N. Nimrod  
Matthew A. Traupman  
Catherine T. Mattes  
QUINN EMANUEL  
URQUHART & SULLIVAN, LLP  
51 Madison Avenue  
New York, NY 10010

*Attorneys for Plaintiffs*  
*Mitsubishi Tanabe Pharma Corp.,*  
*Janssen Pharmaceuticals, Inc. Janssen*  
*Pharmaceutica NV, Janssen Research*  
*and Development, LLC, and Cilag*  
*GmbH International*

# **EXHIBIT A**



US007943582B2

(12) **United States Patent**  
**Nomura et al.**

(10) **Patent No.:** US 7,943,582 B2  
(45) **Date of Patent:** May 17, 2011

(54) **CRYSTALLINE FORM OF  
1-( $\beta$ -D-GLUCOPYRANOSYL)-4-METHYL-3-[5-(4-FLUOROPHENYL)-2-THIENYL]METHYL]BENZENE  
HEMIHYDRATE**

(75) Inventors: **Sumihiro Nomura**, Osaka (JP); **Eiji Kawanishi**, Osaka (JP)

(73) Assignee: **Mitsubishi Tanabe Pharma Corporation**, Osaka-Shi (JP)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 451 days.

(21) Appl. No.: **11/987,670**

(22) Filed: **Dec. 3, 2007**

(65) **Prior Publication Data**

US 2008/0146515 A1 Jun. 19, 2008

**Related U.S. Application Data**

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(30) **Foreign Application Priority Data**

Dec. 4, 2006 (JP) ..... 2006-327019

(51) **Int. Cl.**

*A61K 31/7034* (2006.01)  
*C07H 7/04* (2006.01)

(52) **U.S. Cl.** ..... **514/23; 536/1.11**

(58) **Field of Classification Search** ..... None  
See application file for complete search history.

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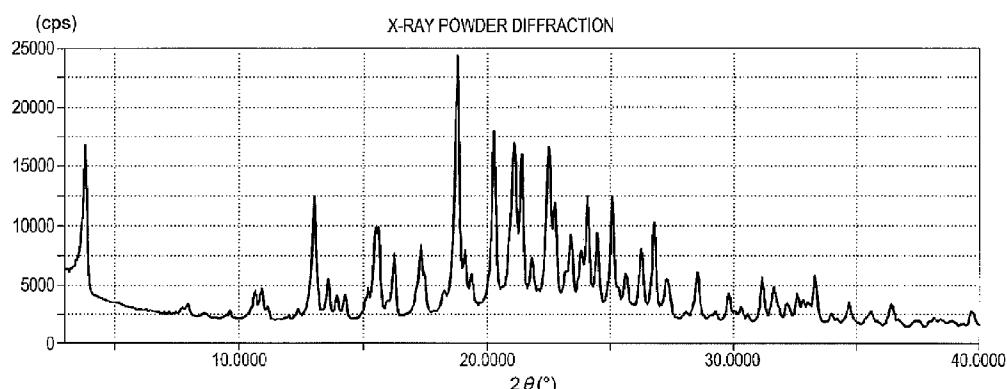
*Primary Examiner* — Eric S Olson

(74) *Attorney, Agent, or Firm* — Birch, Stewart, Kolasch & Birch, LLP

(57) **ABSTRACT**

A novel crystal form of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate, and having favorable characteristics, is characterized by its x-ray powder diffraction pattern and/or by its infra-red spectrum.

**7 Claims, 2 Drawing Sheets**



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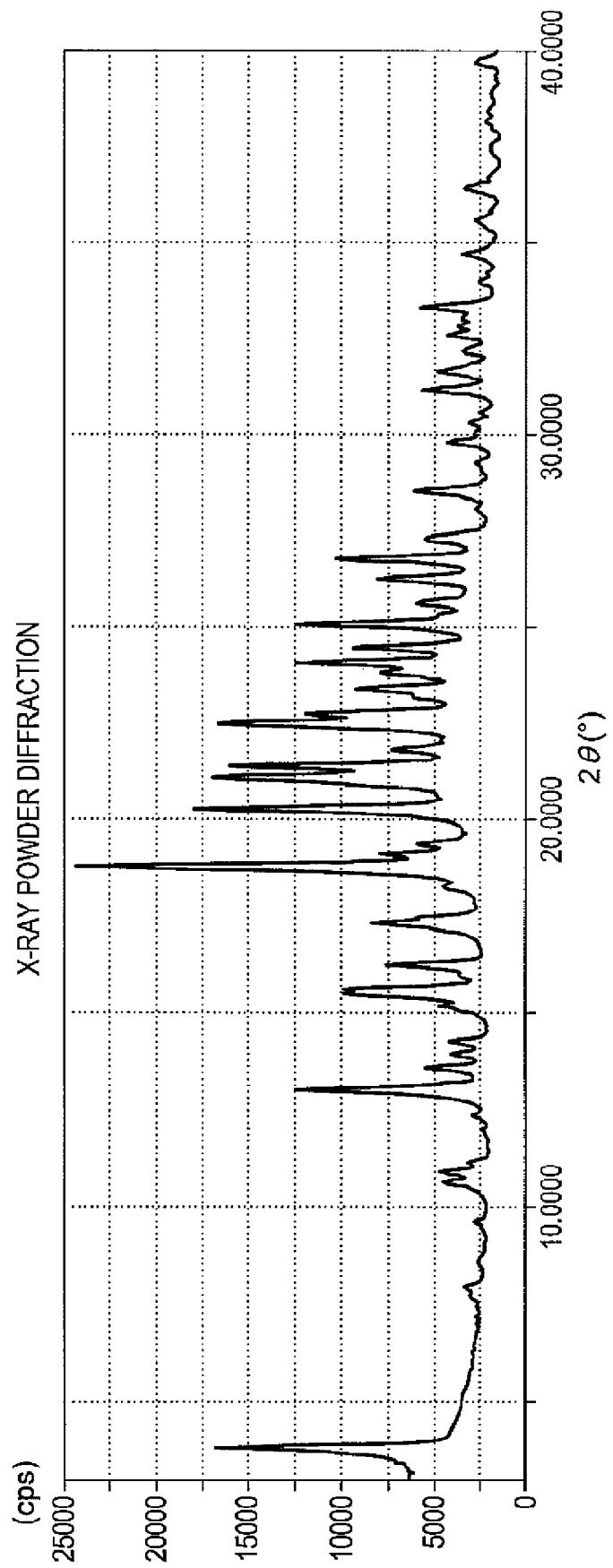
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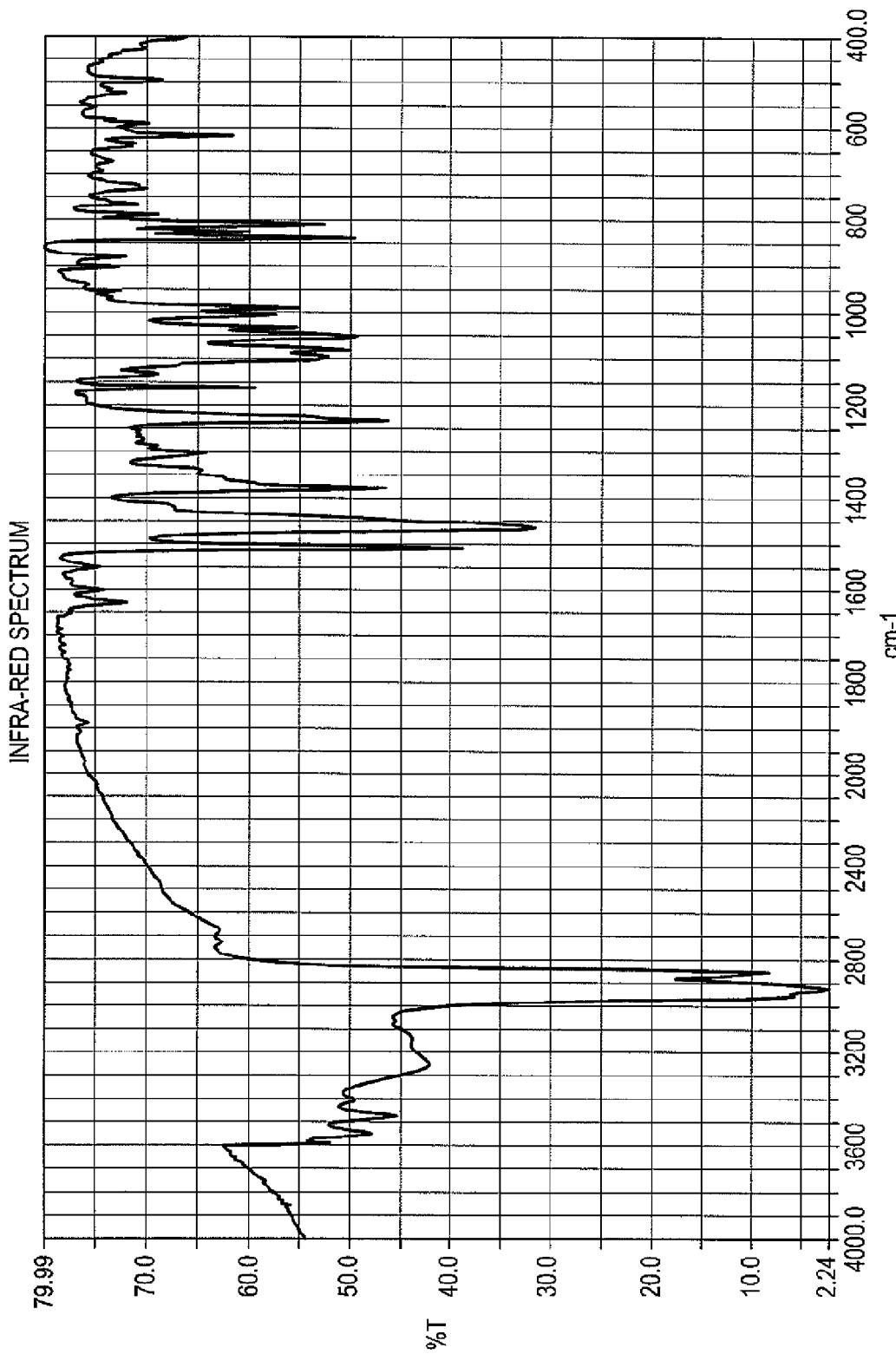
**FIG. 1**

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**FIG.2**

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**CRYSTALLINE FORM OF**  
**1-( $\beta$ -D-GLUCOPYRANSOYL)-4-METHYL-3-**  
**[5-(4-FLUOROPHENYL)-2-**  
**THIENYL]METHYL]BENZENE**  
**HEMIHYDRATE**

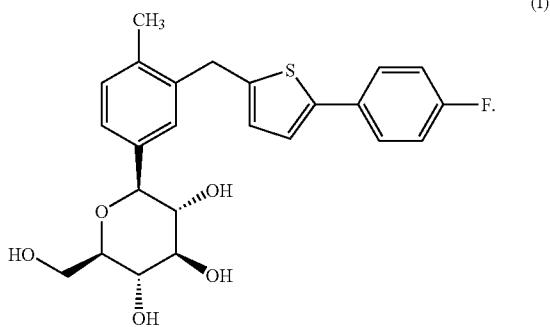
## BACKGROUND OF THE INVENTION

## 1. Field of the Invention

This invention relates to a crystalline form of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate useful as an inhibitor of sodium-dependent glucose transporter, to methods for its preparation and isolation, to pharmaceutical compositions which include the compound and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment.

## 2. Description of the Related Art

WO 2005/012326 pamphlet discloses a class of compounds that are inhibitors of sodium-dependent glucose transporter (SGLT) and thus of therapeutic use for treatment of diabetes, obesity, diabetic complications, and the like. There is described in WO 2005/012326 pamphlet 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene of formula (I):



In general, for commercial use it is important that a product should have good handling qualities. Additionally, there is a need to produce the product in a pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications.

And it is desirable that the product should be in a form that is readily filterable and easily dried.

Additionally, it is economically desirable that the product be stable for extended periods of time without the need for specialized storage conditions.

But there have been difficulties in obtaining a crystal form of the compound of formula (I) from organic solvents.

It has now been discovered that the compound of formula (I) hemihydrate can be produced in a crystalline form in a manner reproducible on a commercial scale.

## SUMMARY OF THE INVENTION

The present invention provides a crystalline form of hemihydrate of the compound of formula (I) as a novel material, in particular in pharmaceutically acceptable form.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1:  
X-ray powder diffraction pattern of the crystalline of hemihydrate of the compound of formula (I).

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FIG. 2:  
Infra-red spectrum of the crystalline of hemihydrate of the compound of formula (I).

## 5 DETAILED DESCRIPTION OF THE INVENTION

The inventors of the present invention have found that the compounds of formula (I) can be crystallized from a water-containing solvent and the crystalline form of hemihydrate of the compounds (I) have good handling qualities and characteristics.

Accordingly, the present invention is directed to:

1. A crystalline of hemihydrate of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.
2. A crystalline of hemihydrate of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene characterized by a powder x-ray diffraction pattern comprising the following 20 values measured using  $\text{CuK}_\alpha$  radiation:  $4.36 \pm 0.2$ ,  $13.54 \pm 0.2$ ,  $16.00 \pm 0.2$ ,  $19.32 \pm 0.2$ ,  $20.80 \pm 0.2$ .
3. A crystalline of hemihydrate of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same X-ray powder diffraction pattern as set out in FIG. 1.
- 25 4. A crystalline of hemihydrate of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same IR spectrum, as set out in FIG. 2.
5. A process for the preparation of a crystalline of hemihydrate of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, which comprises forming a solution of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.
- 30 6. A pharmaceutical composition comprising an effective amount of a crystalline of hemihydrate of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and a pharmaceutically acceptable carrier.
7. A method for treatment or delaying the progression or onset 40 of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline of hemihydrate of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.

As discussed, the present invention includes a certain solid state crystalline form. Several methods for characterizing such forms exist, and the invention should not be limited by the methods chosen or the instrumentation used in characterizing the compounds of the present invention. For example, with regard to x-ray diffraction patterns, the diffraction peak intensities in the experimental patterns can vary, as is known in the art, primarily due to preferred orientation (non-random orientation of the crystals) in the prepared sample. As such, the scope of the present invention must be considered in light of the variability of characterization that is appreciated by those skilled in the art.

## X-Ray Powder Diffraction

The crystalline form of the present invention (I) is characterized by its X-ray powder diffraction pattern. The X-ray diffraction pattern of the crystalline of hemihydrate of the compound (I) was measured on an X-ray diffractometer

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(RINT-TTR III, Rigaku, Tokyo, Japan) with measured using CuK<sub>α</sub> radiation. Methodology of X-ray powder diffraction is as follows:

Scanning rate: 2.00 degree/minute.

Target: CuK<sub>α</sub>.

Voltage: 50 kV.

Current: 300 mA.

Scan range: from 3 to 40.0 degree.

Sampling width: 0.0200 degree.

## Infra-Red Spectrum

The infra-red spectrum of the crystalline form of the present invention in mineral oil comprises the following main peaks: 1626, 1600, 1549, and 1507 cm<sup>-1</sup>.

The infra-red spectrum of crystalline compound (I) hemihydrate is shown in the accompanying drawing in which the ordinate is the transmittance in % and the abscissa is the wavenumber in cm<sup>-1</sup>.

## Thermogravimetric Analysis

The crystalline form of the present invention has been observed to exist in a hemihydrate form. The theoretical water content of the crystalline of the present invention is 1.98%. The thermogravimetric analysis for the crystalline of the present invention shows a mass loss of 1.705%.

Methodology of thermogravimetric analysis is as follows: about 8 mg of compound (I) hemihydrate is weighed and transferred in an aluminum cell holder for TG-50 (Shimadzu, Japan), and then, the thermogravimetric (TG) thermal curve of crystalline compound (I) hemihydrate is determined at a heat rate of 5° C./minute. Typical measuring range is from ambient to 150° C.

The present invention also provides a process for producing the crystalline form of hemihydrate of the compound (I) which comprises forming a solution of compound (I) and precipitating the crystalline form from solution.

Typically, the crystalline of hemihydrate of the compound (I) may be obtained from a mixture of the compound of formula (I), a good solvent and water, optionally containing a poor solvent.

Sometimes some impurities may act as crystallization inhibitors, and impurities need to be removed using a conventional manner, such as silica gel column chromatography. However, the crystalline of hemihydrate of the compound of formula (I) can even be obtained from relatively impure compound (I).

The present invention also provides a pharmaceutical composition comprising the crystalline of hemihydrate of the compound (I) and a pharmaceutically acceptable carrier.

The crystalline compound of the present invention possesses activity as inhibitors of sodium-dependent glucose transporters, and show excellent blood glucose lowering effect.

The crystalline form of the present invention are expected to be useful in the treatment, prevention or delaying the progression or onset of diabetes mellitus (type 1 and type 2 diabetes mellitus, etc.), diabetic complications (such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy), postprandial hyperglycemia, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, atherosclerosis, or hypertension.

The crystalline form of the present invention or a pharmaceutically acceptable salt thereof may be administered either orally or parenterally, and can be used in the form of a suitable pharmaceutical preparation. Suitable pharmaceutical preparations for oral administration include, for example, solid preparations such as tablets, granules, capsules, and powders,

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or solution preparations, suspension preparations, emulsion preparations, and the like. Suitable pharmaceutical preparations for parenteral administration include, for example, suppositories; injection preparations or intravenous drip preparations, using distilled water for injection, physiological saline solution or aqueous glucose solution; and inhalant preparations.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, from about 0.01 mg/kg to about 100 mg/kg body weight (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be given at a dosage of from about 0.01 mg/kg/day to about 100 mg/kg/day (preferably from about 0.01 mg/kg/day to about 50 mg/kg/day and more preferably from about 0.01 mg/kg/day to about 30 mg/kg/day). The method of treating a disorder described in the present invention may also be carried out using a pharmaceutical composition comprising the crystalline form as defined herein and a pharmaceutical acceptable carrier. The dosage form will contain from about 0.01 mg/kg to about 100 mg/kg (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be constituted into any form suitable for the mode of administration selected. The dosages, however, may be varied depending upon administration routes, the requirement of the subjects, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

The crystalline form of the present invention may be used, if necessary, in combination with one or more of other anti-diabetic agents, antihyperglycemic agents and/or agents for treatment of other diseases. The present compounds and these other agents may be administered in the same dosage form, or in a separate oral dosage form or by injection.

The dosage of those agents may vary according to, for example, ages, body weight, conditions of patients, administration routes, and dosage forms.

These pharmaceutical compositions may be orally administered to mammalian species including human beings, apes, and dogs, in the dosage form of, for example, tablet, capsule, granule or powder, or parenterally administered in the form of injection preparation, or intranasally, or in the form of transdermal patch.

The crystalline form of hemihydrate of the compound of formula (I) can be prepared from a mixture of the compound (I), a good solvent and water, optionally containing a poor solvent.

Examples of good solvents which have been found suitable include ketones (e.g., acetone, 2-butanone), esters (e.g., ethyl acetate, methyl acetate), alcohols (e.g., methanol, ethanol, i-propanol), and a mixture of these solvents. Examples of poor solvents include alkanes (e.g., hexane, heptane), aromatic hydrocarbons (e.g., benzene, toluene), ethers (e.g., diethyl ether, dimethyl ether, diisopropyl ether) and a mixture of these solvents.

One preferred preparation of the crystalline form of hemihydrate of the compound of formula (I) typically involves dissolving in a good solvent (e.g., ketones or esters) crude or amorphous compound of formula (I) prepared in accordance with the procedures described in WO 2005/012326 pamphlet, and adding water and a poor solvent (e.g., alkanes or ethers) to the resulting solution, followed by filtration.

In case that a good solvent is soluble in water, a poor solvent needs not be used and water may be added to the

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solution of the compound of formula (I) in the good solvent so the solubility of the compound of formula (I) can be decreased in the solution.

In case that a poor solvent is used, water is preferably used in amount of 1 to 10 molar equivalents to the compound of formula (I), the good solvent is preferably used in amount of 10 to 100 times of volume of water, and the poor solvent is preferably used in amount of 0.1 to 10 times of volume of the good solvent.

The precise conditions under which the crystalline of hemihydrate of the compound (I) is formed may be empirically determined.

Under these conditions, crystallization can preferably be carried out at a lowered, ambient or elevated temperature.

The crystalline form of hemihydrate of the compound of formula (I) is significantly easier to isolate than amorphous form of the compound and can be filtered from the crystallization medium after cooling, and washed and dried. Also, the crystalline form of the present invention is more stable than the amorphous form of the compound of formula (I).

## EXAMPLES

## Example 1

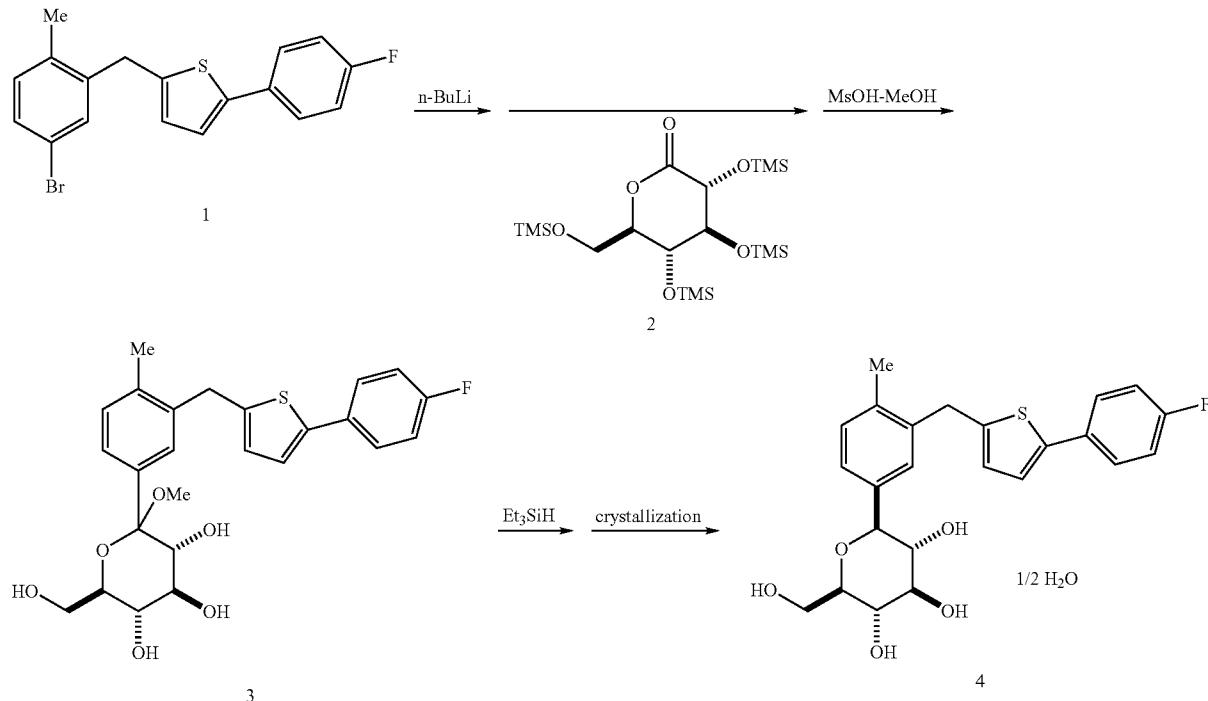
Crystalline 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate

1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene was prepared in a similar manner as described in WO 2005/012326.

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under argon atmosphere, and the mixture was stirred for 20 minutes at the same temperature. Thereto was added a solution of 2 (34.0 g) in toluene (240 ml) dropwise at the same temperature, and the mixture was further stirred for 1 hour at the same temperature. Subsequently, thereto was added a solution of methanesulfonic acid (21.0 g) in methanol (480 ml) dropwise, and the resulting mixture was allowed to warm to room temperature and stirred for 17 hours. The mixture was cooled under ice—water cooling, and thereto was added a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted with ethyl acetate, and the combined organic layer was washed with brine and dried over magnesium sulfate. The insoluble was filtered off and the solvent was evaporated under reduced pressure. The residue was triturated with toluene (100 ml)—hexane (400 ml) to give 1-(1-methoxyglucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene (3) (31.6 g). APCI-Mass m/Z 492 (M+NH<sub>4</sub>).

(2) A solution of 3 (63.1 g) and triethylsilane (46.4 g) in dichloromethane (660 ml) was cooled by dry ice-acetone bath under argon atmosphere, and thereto was added dropwise boron trifluoride•ethyl ether complex (50.0 ml), and the mixture was stirred at the same temperature. The mixture was allowed to warm to 0° C. and stirred for 2 hours. At the same temperature, a saturated aqueous sodium hydrogen carbonate solution (800 ml) was added, and the mixture was stirred for 30 minutes. The organic solvent was evaporated under reduced pressure, and the residue was poured into water and extracted with ethyl acetate twice. The organic layer was washed with water twice, dried over magnesium sulfate and treated with activated carbon. The insoluble was filtered off



(1) To a solution of 5-bromo-1-[5-(4-fluorophenyl)-2-thienylmethyl]-2-methylbenzene (1, 28.9 g) in tetrahydrofuran (480 ml) and toluene (480 ml) was added n-butyllithium (1.6M hexane solution, 50.0 ml) dropwise at -67 to -70° C.

and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (300 ml), and thereto were added diethyl ether (600 ml) and H<sub>2</sub>O (6 ml). The mixture was stirred at room temperature overnight, and the

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precipitate was collected, washed with ethyl acetate-diethyl ether (1:4) and dried under reduced pressure at room temperature to give 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate (33.5 g) as colorless crystals. mp 98-100° C. APCI-Mass m/Z 462 (M+NH<sub>4</sub>). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ 2.26 (3H, s), 3.13-3.28 (4H, m), 3.44 (1H, m), 3.69 (1H, m), 3.96 (1H, d, J=9.3 Hz), 4.10, 4.15 (each 1H, d, J=16.0 Hz), 4.43 (1H, t, J=5.8 Hz), 4.72 (1H, d, J=5.6 Hz), 4.92 (2H, d, J=4.8 Hz), 6.80 (1H, d, J=3.5 Hz), 7.11-7.15 (2H, m), 7.18-7.25 (3H, m), 7.28 (1H, d, J=3.5 Hz), 7.59 (2H, dd, J=8.8, 5.4 Hz). Anal. Calcd. for C<sub>24</sub>H<sub>25</sub>FO<sub>5</sub>S·0.5H<sub>2</sub>O: C, 63.56; H, 5.78; F, 4.19; S, 7.07. Found: C, 63.52; H, 5.72; F, 4.08; S, 7.00.

## Example 2

An amorphous powder of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene (1.62 g) was dissolved in acetone (15 ml), and thereto were added H<sub>2</sub>O (30 ml) and a crystalline seed. The mixture was stirred at room temperature for 18 hours, and the precipitate was collected, washed with acetone-H<sub>2</sub>O (1:4, 30 ml) and dried under reduced pressure at room temperature to give 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate (1.52 g) as colorless crystals. mp 97-100° C.

The invention claimed is:

1. A crystalline form of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate.

2. A crystalline form of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1, having a powder x-ray diffraction pattern comprising the following 2θ values measured using CuK<sub>α</sub> radiation: 4.36±0.2, 13.54±0.2, 16.00±0.2, 19.32±0.2, and 20.80±0.2.

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3. A crystalline form of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1, having substantially the same X-ray diffraction pattern as set out in FIG. 1.

4. A crystalline form of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1, having substantially the same IR spectrum, as set out in FIG. 2.

5. A process for the preparation of a crystalline form of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1, which comprises forming a solution of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.

6. A pharmaceutical composition comprising an effective amount of a crystalline form of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1 and a pharmaceutically acceptable carrier.

7. A method for treatment or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline form of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1 to a subject in need thereof.

\* \* \* \* \*

# **EXHIBIT B**



US008513202B2

(12) **United States Patent**  
**Nomura et al.**

(10) **Patent No.:** **US 8,513,202 B2**  
(45) **Date of Patent:** **\*Aug. 20, 2013**

(54) **CRYSTALLINE FORM OF**  
**1-( $\beta$ -D-GLUCOPYRANOSYL)-4-METHYL-**  
**3-[5-(4-FLUOROPHENYL)-2-THIENYL-**  
**METHYL]BENZENE HEMIHYDRATE**

(75) Inventors: **Sumihiro Nomura**, Osaka (JP); **Eiji Kawanishi**, Osaka (JP)

(73) Assignee: **Mitsubishi Tanabe Pharma Corporation**, Osaka-Shi (JP)

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This patent is subject to a terminal disclaimer.

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(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**  
**A61K 31/7034** (2006.01)  
**C07H 7/04** (2006.01)

(52) **U.S. Cl.**  
CPC ..... **A61K 31/7034** (2013.01); **C07H 7/04** (2013.01)  
USPC ..... **514/23**; 536/122

(58) **Field of Classification Search**

None

See application file for complete search history.

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*Primary Examiner* — Eric S Olson

(74) *Attorney, Agent, or Firm* — Birch, Stewart, Kolasch & Birch, LLP

(57) **ABSTRACT**

A novel crystal form of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate, and having favorable characteristics, is characterized by its x-ray powder diffraction pattern and/or by its infra-red spectrum.

**5 Claims, 2 Drawing Sheets**

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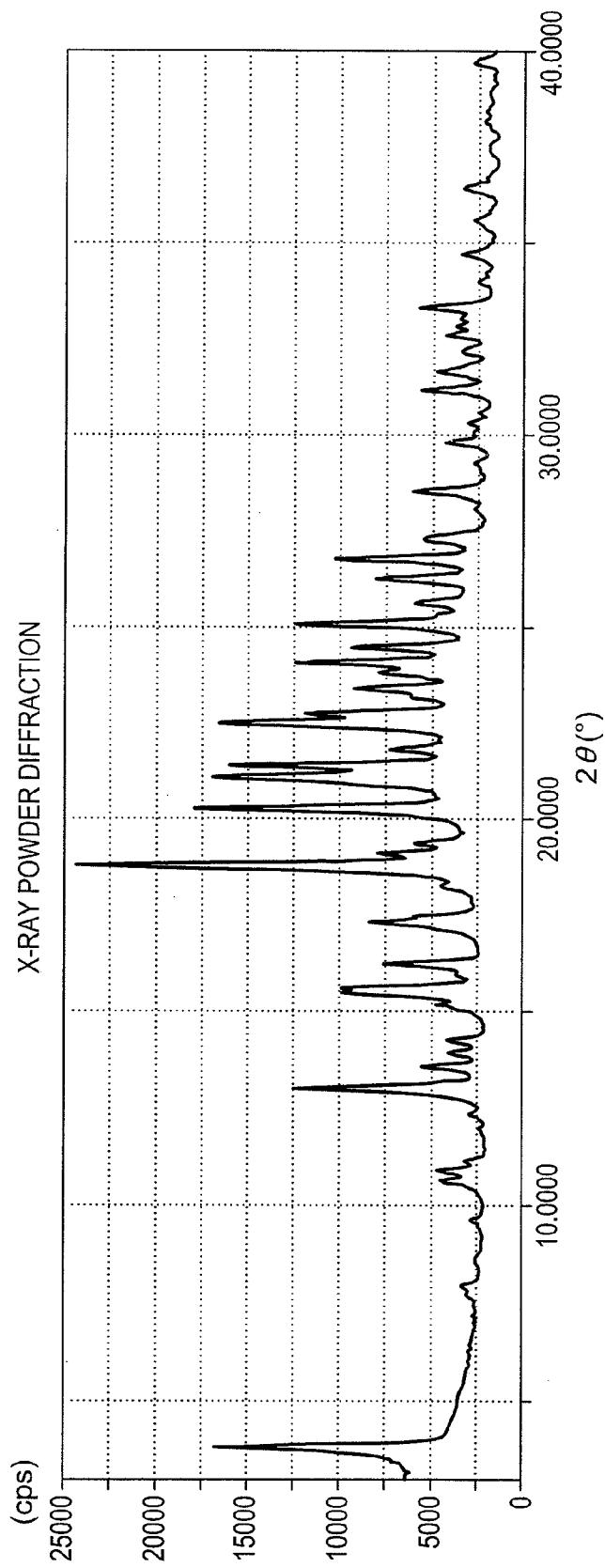
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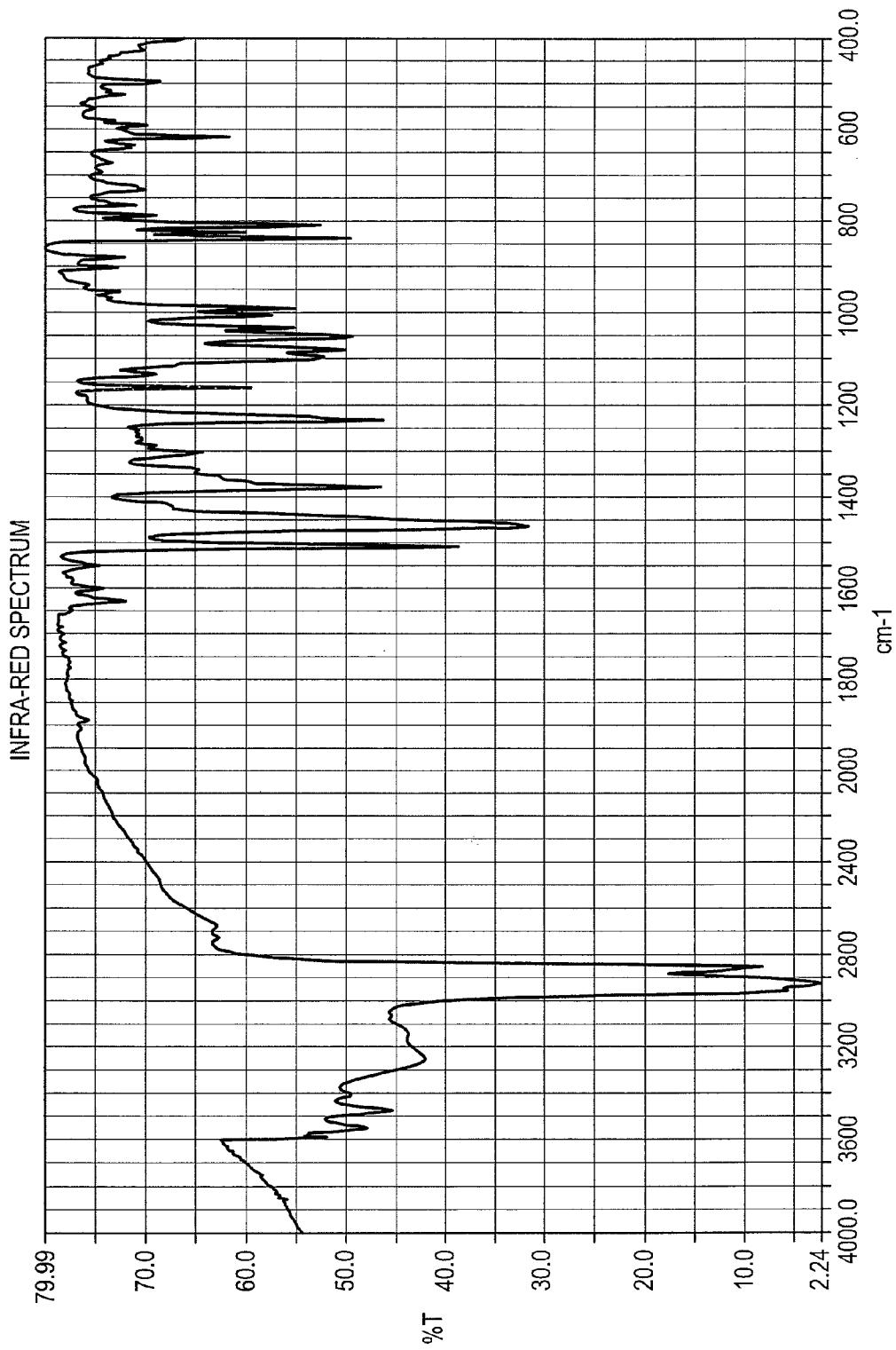
**FIG. 1**

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**FIG. 2**

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## 1

**CRYSTALLINE FORM OF  
1-( $\beta$ -D-GLUCOPYRANOSYL)-4-METHYL-3-  
[5-(4-FLUOROPHENYL)-2-THIENYL-  
METHYL]BENZENE HEMIHYDRATE**

This application is a Continuation of U.S. application Ser. No. 11/987,670 filed Dec. 3, 2007, which issued as U.S. Pat. No. 7,943,582 on May 17, 2011, which claims the benefit of priority under 35 U.S.C. §119(e) of U.S. Application No. 60/868,426, filed Dec. 4, 2006. U.S. application Ser. No. 11/987,670 also claims the benefit of priority of JP 2006-327019, filed Dec. 4, 2006. The entire content of each of the above-identified applications is hereby incorporated by reference.

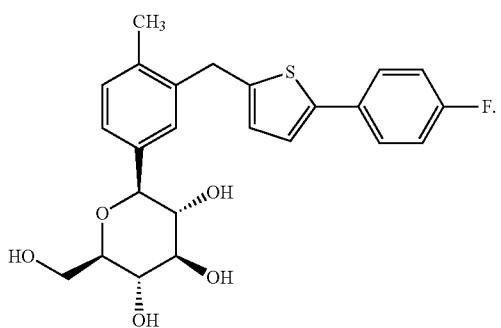
## BACKGROUND OF THE INVENTION

## 1. Field of the Invention

This invention relates to a crystalline form of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate useful as an inhibitor of sodium-dependent glucose transporter, to methods for its preparation and isolation, to pharmaceutical compositions which include the compound and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment.

## 2. Description of the Related Art

WO 2005/012326 pamphlet discloses a class of compounds that are inhibitors of sodium-dependent glucose transporter (SGLT) and thus of therapeutic use for treatment of diabetes, obesity, diabetic complications, and the like. There is described in WO 2005/012326 pamphlet 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene of formula (I):



In general, for commercial use it is important that a product should have good handling qualities. Additionally, there is a need to produce the product in a pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications.

And it is desirable that the product should be in a form that is readily filterable and easily dried. Additionally, it is economically desirable that the product be stable for extended periods of time without the need for specialized storage conditions.

But there have been difficulties in obtaining a crystal form of the compound of formula (I) from organic solvents.

It has now been discovered that the compound of formula (I) hemihydrate can be produced in a crystalline form in a manner reproducible on a commercial scale.

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## SUMMARY OF THE INVENTION

The present invention provides a crystalline form of hemihydrate of the compound of formula (I) as a novel material, in particular in pharmaceutically acceptable form.

## BRIEF DESCRIPTION OF THE DRAWINGS

## FIG. 1:

X-ray powder diffraction pattern of the crystalline of hemihydrate of the compound of formula (I).

## FIG. 2:

Infra-red spectrum of the crystalline of hemihydrate of the compound of formula (I).

## DETAILED DESCRIPTION OF THE INVENTION

The inventors of the present invention have found that the compounds of formula (I) can be crystallized from a water-containing solvent and the crystalline form of hemihydrate of the compounds (I) have good handling qualities and characteristics.

Accordingly, the present invention is directed to:

1. A crystalline of hemihydrate of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.
2. A crystalline of hemihydrate of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene characterized by a powder x-ray diffraction pattern comprising the following 20 values measured using  $\text{CuK}_\alpha$  radiation: 4.36±0.2, 13.54±0.2, 16.00±0.2, 19.32±0.2, 20.80±0.2.
3. A crystalline of hemihydrate of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same X-ray powder diffraction pattern as set out in FIG. 1.
4. A crystalline of hemihydrate of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same IR spectrum, as set out in FIG. 2.
5. A process for the preparation of a crystalline of hemihydrate of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, which comprises forming a solution of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.
6. A pharmaceutical composition comprising an effective amount of a crystalline of hemihydrate of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and a pharmaceutically acceptable carrier.
7. A method for treatment or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline of hemihydrate of 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.
8. As discussed, the present invention includes a certain solid state crystalline form. Several methods for characterizing such forms exist, and the invention should not be limited by the methods chosen or the instrumentation used in characterizing the compounds of the present invention. For example, with regard to x-ray diffraction patterns, the diffraction peak intensities in the experimental patterns can vary, as is known in the art, primarily due to preferred orientation (non-random

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orientation of the crystals) in the prepared sample. As such, the scope of the present invention must be considered in light of the variability of characterization that is appreciated by those skilled in the art.

## X-Ray Powder Diffraction

The crystalline form of the present invention (I) is characterized by its X-ray powder diffraction pattern. The X-ray diffraction pattern of the crystalline of hemihydrate of the compound (I) was measured on an X-ray diffractometer (RINT-TTR III, Rigaku, Tokyo, Japan) with measured using CuK $\alpha$  radiation. Methodology of X-ray powder diffraction is as follows:

Scanning rate: 2.00 degree/minute.

Target: CuK $\alpha$ .

Voltage: 50 kV.

Current: 300 mA.

Scan range: from 3 to 40.0 degree.

Sampling width: 0.0200 degree.

## Infra-Red Spectrum

The infra-red spectrum of the crystalline form of the present invention in mineral oil comprises the following main peaks: 1626, 1600, 1549, and 1507  $\text{cm}^{-1}$ .

The infra-red spectrum of crystalline compound (I) hemihydrate is shown in the accompanying drawing in which the ordinate is the transmittance in % and the abscissa is the wavenumber in  $\text{cm}^{-1}$ .

## Thermogravimetric Analysis

The crystalline form of the present invention has been observed to exist in a hemihydrate form. The theoretical water content of the crystalline of the present invention is 1.98%. The thermogravimetric analysis for the crystalline of the present invention shows a mass loss of 1.705%.

Methodology of thermogravimetric analysis is as follows: about 8 mg of compound (I) hemihydrate is weighed and transferred in an aluminum cell holder for TG-50 (Shimadzu, Japan), and then, the thermogravimetric (TG) thermal curve of crystalline compound (I) hemihydrate is determined at a heat rate of 5° C./minute. Typical measuring range is from ambient to 150° C.

The present invention also provides a process for producing the crystalline form of hemihydrate of the compound (I) which comprises forming a solution of compound (I) and precipitating the crystalline form from solution.

Typically, the crystalline of hemihydrate of the compound (I) may be obtained from a mixture of the compound of formula (I), a good solvent and water, optionally containing a poor solvent.

Sometimes some impurities may act as crystallization inhibitors, and impurities need to be removed using a conventional manner, such as silica gel column chromatography. However, the crystalline of hemihydrate of the compound of formula (I) can even be obtained from relatively impure compound (I).

The present invention also provides a pharmaceutical composition comprising the crystalline of hemihydrate of the compound (I) and a pharmaceutically acceptable carrier.

The crystalline compound of the present invention possesses activity as inhibitors of sodium-dependent glucose transporters, and show excellent blood glucose lowering effect.

The crystalline form of the present invention are expected to be useful in the treatment, prevention or delaying the progression or onset of diabetes mellitus (type 1 and type 2 diabetes mellitus, etc.), diabetic complications (such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy), postprandial hyperglycemia, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia,

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elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, atherosclerosis, or hypertension.

The crystalline form of the present invention or a pharmaceutically acceptable salt thereof may be administered either orally or parenterally, and can be used in the form of a suitable pharmaceutical preparation. Suitable pharmaceutical preparations for oral administration include, for example, solid preparations such as tablets, granules, capsules, and powders, or solution preparations, suspension preparations, emulsion preparations, and the like. Suitable pharmaceutical preparations for parenteral administration include, for example, suppositories; injection preparations or intravenous drip preparations, using distilled water for injection, physiological saline solution or aqueous glucose solution; and inhalant preparations.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, from about 0.01 mg/kg to about 100 mg/kg body weight (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be given at a dosage of from about 0.01 mg/kg/day to about 100 mg/kg/day (preferably from about 0.01 mg/kg/day to about 50 mg/kg/day and more preferably from about 0.01 mg/kg/day to about 30 mg/kg/day). The method of treating a disorder described in the present invention may also be carried out using a pharmaceutical composition comprising the crystalline form as defined herein and a pharmaceutical acceptable carrier. The dosage form will contain from about 0.01 mg/kg to about 100 mg/kg (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be constituted into any form suitable for the mode of administration selected. The dosages, however, may be varied depending upon administration routes, the requirement of the subjects, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

The crystalline form of the present invention may be used, if necessary, in combination with one or more of other anti-diabetic agents, antihyperglycemic agents and/or agents for treatment of other diseases. The present compounds and these other agents may be administered in the same dosage form, or in a separate oral dosage form or by injection.

The dosage of those agents may vary according to, for example, ages, body weight, conditions of patients, administration routes, and dosage forms.

These pharmaceutical compositions may be orally administered to mammalian species including human beings, apes, and dogs, in the dosage form of, for example, tablet, capsule, granule or powder, or parenterally administered in the form of injection preparation, or intranasally, or in the form of transdermal patch.

The crystalline form of hemihydrate of the compound of formula (I) can be prepared from a mixture of the compound (I), a good solvent and water, optionally containing a poor solvent.

Examples of good solvents which have been found suitable include ketones (e.g., acetone, 2-butanone), esters (e.g., ethyl acetate, methyl acetate), alcohols (e.g., methanol, ethanol, i-propanol), and a mixture of these solvents. Examples of poor solvents include alkanes (e.g., hexane, heptane), aromatic hydrocarbons (e.g., benzene, toluene), ethers (e.g., diethyl ether, dimethyl ether, diisopropyl ether) and a mixture of these solvents.

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One preferred preparation of the crystalline form of hemihydrate of the compound of formula (I) typically involves dissolving in a good solvent (e.g., ketones or esters) crude or amorphous compound of formula (I) prepared in accordance with the procedures described in WO 2005/012326 pamphlet, and adding water and a poor solvent (e.g., alkanes or ethers) to the resulting solution, followed by filtration.

In case that a good solvent is soluble in water, a poor solvent needs not be used and water may be added to the solution of the compound of formula (I) in the good solvent so the solubility of the compound of formula (I) can be decreased in the solution.

In case that a poor solvent is used, water is preferably used in amount of 1 to 10 molar equivalents to the compound of formula (I), the good solvent is preferably used in amount of 10 to 100 times of volume of water, and the poor solvent is preferably used in amount of 0.1 to 10 times of volume of the good solvent.

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The crystalline form of hemihydrate of the compound of formula (I) is significantly easier to isolate than amorphous form of the compound and can be filtered from the crystallization medium after cooling, and washed and dried. Also, the crystalline form of the present invention is more stable than the amorphous form of the compound of formula (I).

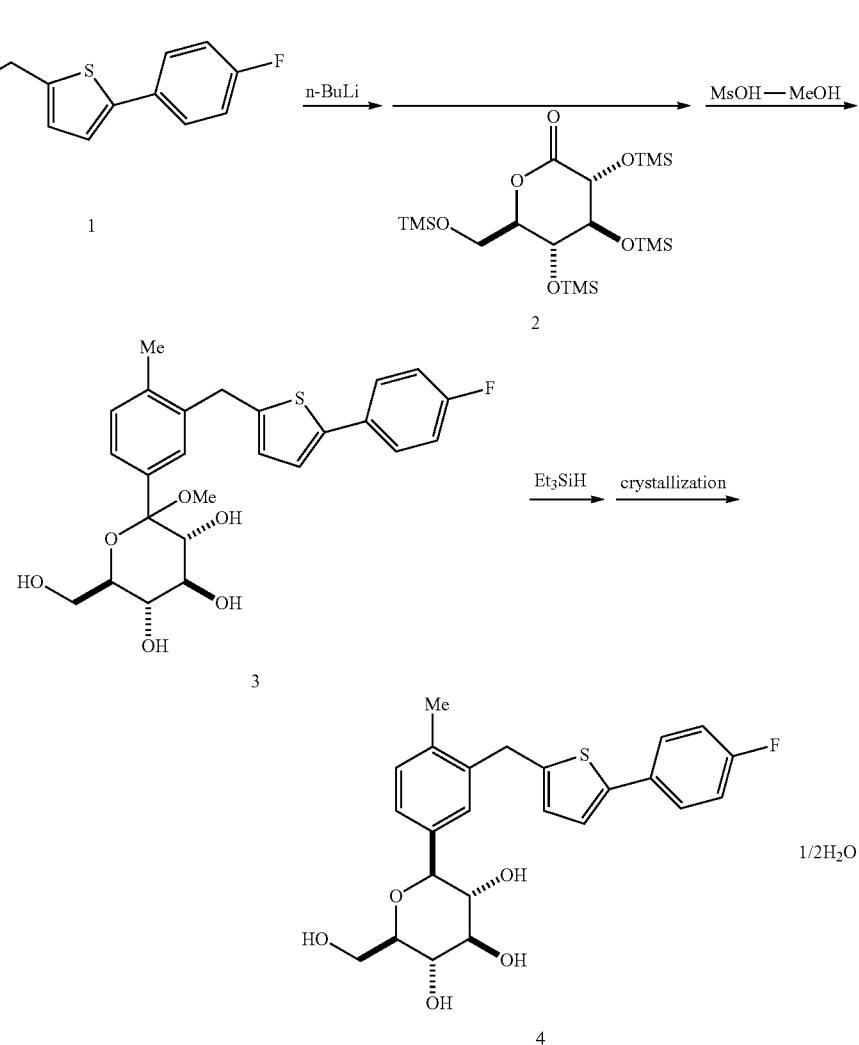
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## EXAMPLES

## Example 1

Crystalline 1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate

1-( $\beta$ -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene was prepared in a similar manner as described in WO 2005/012326.



The precise conditions under which the crystalline of hemihydrate of the compound (I) is formed may be empirically determined.

Under these conditions, crystallization can preferably be carried out at a lowered, ambient or elevated temperature.

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(1) To a solution of 5-bromo-1-[5-(4-fluorophenyl)-2-thienylmethyl]-2-methylbenzene (1, 28.9 g) in tetrahydrofuran (480 ml) and toluene (480 ml) was added  $n$ -butyllithium (1.6M hexane solution, 50.0 ml) dropwise at  $-67$  to  $-70^\circ\text{C}$ . under argon atmosphere, and the mixture was stirred for 20

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minutes at the same temperature. Thereto was added a solution of 2 (34.0 g) in toluene (240 ml) dropwise at the same temperature, and the mixture was further stirred for 1 hour at the same temperature. Subsequently, thereto was added a solution of methanesulfonic acid (21.0 g) in methanol (480 ml) dropwise, and the resulting mixture was allowed to warm to room temperature and stirred for 17 hours. The mixture was cooled under ice—water cooling, and thereto was added a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted with ethyl acetate, and the combined organic layer was washed with brine and dried over magnesium sulfate. The insoluble was filtered off and the solvent was evaporated under reduced pressure. The residue was triturated with toluene (100 ml)—hexane (400 ml) to give 1-(1-methoxyglucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene (3) (31.6 g). APCI-Mass m/Z 492 (M+NH<sub>4</sub>).

(2) A solution of 3 (63.1 g) and triethylsilane (46.4 g) in dichloromethane (660 ml) was cooled by dry ice—acetone bath under argon atmosphere, and thereto was added dropwise boron trifluoride.ethyl ether complex (50.0 ml), and the mixture was stirred at the same temperature. The mixture was allowed to warm to 0° C. and stirred for 2 hours. At the same temperature, a saturated aqueous sodium hydrogen carbonate solution (800 ml) was added, and the mixture was stirred for 30 minutes. The organic solvent was evaporated under reduced pressure, and the residue was poured into water and extracted with ethyl acetate twice. The organic layer was washed with water twice, dried over magnesium sulfate and treated with activated carbon. The insoluble was filtered off and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (300 ml), and thereto were added diethyl ether (600 ml) and H<sub>2</sub>O (6 ml). The mixture was stirred at room temperature overnight, and the precipitate was collected, washed with ethyl acetate—diethyl ether (1:4) and dried under reduced pressure at room temperature to give 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene hemihydrate (33.5 g) as colorless crystals. mp 98-100° C. APCI-Mass m/Z 462 (M+NH<sub>4</sub>). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ 2.26 (3H, s), 3.13-3.28 (4H, m), 3.44 (1H, m), 3.69 (1H, m), 3.96 (1H, d, J=9.3 Hz), 4.10, 4.15 (each 1H, d, J=16.0 Hz), 4.43 (1H, t, J=5.8 Hz), 4.72 (1H, d, J=5.6 Hz), 4.92 (2H, d, J=4.8 Hz), 6.80 (1H, d, J=3.5 Hz), 7.11-7.15 (2H, m), 7.18-7.25 (3H, m), 7.28 (1H, d, J=3.5 Hz), 7.59 (2H, dd, J=8.8, 5.4 Hz). Anal. Calcd. for C<sub>24</sub>H<sub>25</sub>FO<sub>5</sub>S·0.5H<sub>2</sub>O: C, 63.56; H, 5.78; F, 4.19; S, 7.07. Found: C, 63.52; H, 5.72; F, 4.08; S, 7.00.

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## Example 2

An amorphous powder of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene (1.62 g) was dissolved in acetone (15 ml), and thereto were added H<sub>2</sub>O (30 ml) and a crystalline seed. The mixture was stirred at room temperature for 18 hours, and the precipitate was collected, washed with acetone—H<sub>2</sub>O (1:4, 30 ml) and dried under reduced pressure at room temperature to give 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene hemihydrate (1.52 g) as colorless crystals. mp 97-100° C.

The invention claimed is:

1. A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene hemihydrate having an infra-red spectrum in mineral oil comprising the following main peaks: 1626, 1600, 1549, and 1507 cm<sup>-1</sup>.
2. A process for the preparation of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene hemihydrate of claim 1, which comprises forming a solution of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.
3. A pharmaceutical composition comprising an effective amount of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene hemihydrate of claim 1 and a pharmaceutically acceptable carrier.
4. A method for treatment or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene hemihydrate of claim 1 to a subject in need thereof.
5. A method for inhibiting a sodium-dependent glucose transporter in a mammal in need thereof, comprising administering to said mammal a therapeutically effective amount of the crystalline form of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene of claim 1.

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